TRIAL WATCH

Oral mucositis relief

Amgen (http://www.amgentrials.com/) announced in January that recombinant human keratinocyte growth factor (rHu-KGF) decreased the duration and incidence of severe oral mucositis in a Phase III study of patients undergoing bone-marrow transplantation for haematological malignancies such as lymphoma, multiple myeloma and leukaemia.

Oral mucositis — inflammation and ulceration of the moist tissue that lines the mouth — occurs in approximately 40% of patients who receive chemotherapy or radiation therapy. Symptoms vary from pain and discomfort to an inability to take food or fluid, and patients are also prone to opportunistic mouth infections.

Amgen has been studying the ability of rHu-KGF to protect epithelial cells from injury caused by anticancer treatments. KGF stimulates the proliferation and development of epithelial cells, including the cells that line the gastrointestinal tract. Preliminary results from the randomized, double-blind trial, which is now closed to recruitment, showed a significant decrease in both the duration and incidence of severe mucositis. rHu-KGF was well tolerated in these patients.

Aesgen-14 (AES-14), developed by Aesgen, Inc., is also in Phase III clinical trials for oral mucositis. The therapy has recently been granted fast-track status from the US Food and Drug Administration, which expedites the regulatory review and approval process.

AES-14 is a mouth-rinse suspension that contains (L) glutamine in a proprietary vehicle that increases cellular glutamine uptake, and is used several times per day during chemotherapy. Randomized, placebo-controlled trials in the United States and elsewhere include patients with oral mucositis who are receiving chemotherapy for breast cancer. Preliminary data indicate that AES-14 significantly reduced the emergence, severity and duration of mucositis.

HPV risk revealed

Infection with human papillomavirus (HPV) is the main cause of cervical cancer, but little is known about the level of risk associated with different HPV types. More than 80 HPV types have been identified, but, so far, only 11 are consistently classified as high risk, and only types 16 and 18 are considered to be *bona fide* human carcinogens. In the 6 February issue of *The New England Journal of Medicine*, Nubia Muñoz *et al*. studied data from 11 case–control studies performed in nine countries. The studies involved 1,918 women with histologically confirmed squamous-cell cervical cancer and 1,928 control women. In addition to HPV types 16 and 18, the authors reported that 13 other types should be considered high risk and 3 types should be considered as "probably carcinogenic".

In the study, cervical cells and tumour biopsy specimens were collected from untreated patients with newly diagnosed invasive or *in situ* squamous-cell cervical cancer. HPV DNA was detected in more than 90% of patients with cervical cancer and in roughly 15% of controls. The most common HPV types detected, in descending order of frequency, were types 16, 18, 45, 31, 33, 52, 58 and 35. Among controls, types 16, 18, 45, 31, 6, 58, 35 and 33 were the most common. The pooled odds ratio for cervical cancer associated with the presence of any HPV was 158.2. The association with the most and least common HPV types was similar, with an odds ratios of more than 45. The findings indicate that an effective vaccine against the five most common HPV types could prevent almost 90% of cervical cancer cases worldwide.

ORIGINAL RESEARCH PAPER Muñoz, N. *et al*. Epidemiological classification of human papillomavirus types associated with cervical cancer. *N. Engl. J. Med.* **348**, 518–527 (2003)

MODEL ORGANISMS

An unusual model

Zebrafish are a surprisingly useful model system for studying cancer. They develop tumours that are similar to those in humans, yet they are genetically tractable. However, their use has been hampered by the lack of a stable line of transgenic, tumour-bearing animals. This obstacle has now been overcome by Thomas Look and colleagues, who have generated transgenic fish that express the mouse *Myc* oncogene and that succumb to T-cell leukaemia.

The *Myc* transgene — expressed behind the *Rag2* promoter, which causes lymphoid-specific gene expression — was microinjected into wild-type zebrafish embryos, either with or without a green fluorescent protein (GFP) tag. Of the resulting fish, 5–6% developed tumours, regardless of whether GFP was present, and this proportion corresponded with the number of fish that expressed GFP if it was injected alone, which indicates that almost every fish that expresses the transgene develops cancer.

The fish developed tumours in the thymus, which is adjacent to the gills. Lymphoblasts had also infiltrated the kidney marrow — the site of definitive haematopoiesis in the fish — and several other sites. Quantitative analysis showed that six times more lymphoblasts were present in the kidney and spleen of the leukaemic fish than in wild-type fish.

Next, gene-expression profiles were analysed to determine the tumour lineage. Interestingly, T-cell-specific, but not B-cell-specific, genes were expressed in these tumours. Furthermore, two out of three of the examined tumours had clonal rearrangements in the *zTcr*-α gene, which both confirms the thymic origin and indicates that additional mutations are required for the leukaemia phenotype.

The transplantability of these tumours was assessed by intraperitoneally injecting leukaemic lymphoblasts into wild-type fish. Leukaemic cells were detectable at the site of injection within 7 days, and soon spread throughout the peritoneal cavity, eventually homing to the thymus.

The short life of these fish — due to cancer development — means that the line must be propagated by *in vitro* fertilization. Sperm taken from male leukaemic fish were used to fertilize eggs from wild-type females, and the resultant offspring developed leukaemia within 4–6 weeks. The use of regulatable promoters would solve this technical problem.

So, this cancer model is the first of its kind, and can now be used in forward screens that search for modifiers of the Myc-induced leukaemia phenotype. We await new discoveries with interest.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Langenau, D. M. *et al.* Myc-induced T cell leukemia in transgenic zebrafish. *Science* **299**, 887–890 (2003)

WEB SITE

Thomas Look's lab: http://research.dfci.harvard.edu/looklab/